REMARKS

Elected claims 1-6, 9-14, 17-24 and 27-31 are pending in the application and under examination. Claim 27 is cancelled herein. Claims 1-4, 6, 9, 11-12, 17-20, 23-24, and 28-31 are amended herein. The Applicants wish to thank the Examiner for rejoining SEQ ID NOs: 1 and 10 as a single invention group.

The specification has been amended herein to correct minor typographical errors and to reflect a change in the numbering of the drawings. The Brief Description of the Drawings was also amended accordingly.

Claims 1-4, 6, 9, 11-12, 17-20, 23-24, and 28-31 have been amended herein to more clearly define the present invention, and to achieve consistency throughout the claims. Support for the claim amendments can be found throughout the specification. No new matter has been added. The amendments made herein are made for purposes of clarification, do not narrow the claims, and are not for reasons substantially related to patentability.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendments. The attached pages are captioned "Version With Markings to Show Changes Made."

I. Objections to the Specification and Claims

The disclosure was objected to because an embedded hyperlink to an Internet address

withdrawn.

The disclosure was also objected to because Figures 5, 6, and 7 were allegedly not described in the Brief Description of the Drawings. The Brief Description of the Drawings has been corrected. Applicants note that the correction was due to renumbering original Figure 1 to include Figure 1-4, at which time originally referenced Figures 2, 3, and 4 should have been renumbered to Figures 5, 6, and 7. No new matter was added. The amended Brief Description of the Drawings overcomes the grounds of the objection. Applicants respectfully request that the objection be withdrawn.

II. Claim Rejections Under 35 U.S.C. §102 And the Art Cited Therein

Claims 24 and 27 stand rejected under 35 U.S.C. §102(b) as anticipated by Newman *et al.* (not "Lansing *et al.*") (Plant Physiology 106:1241-1255 (1994)). A copy of Newman et al. (1994) is enclosed for the Examiner's convenience. As can be seen, the Newman reference does not disclose any relevant sequence information and so cannot in and of itself form the basis of a rejection under 35 U.S.C. §102(b). Applicants respectfully note that the Office Action, however, does not directly cite to this publication, but rather to sequences provided in a search the Examiner apparently conducted against sequences on the Genbank database. The sequence accession number AA394594 is directly cited, and provided with the Office Action. The date on which this sequence was entered into the Genbank database, as the Office Action correctly indicates, was 1997, specifically October 30, 1997, which must be considered the publication date of record for this sequence.

Applicants' claims at issue are entitled to a priority date of September 25, 1998.

Pending claims are entitled to PCT/US99/22363 filed September 24, 1999, which claimed

Accession Number AA394594 cannot be cited as 102(b) art, and thus, the rejection under

102(b) on the basis of those sequences is improper. Applicants respectfully request that the improper rejection be withdrawn. Applicants additionally respectfully reiterate that claim 27 has been cancelled in an effort to further prosecution; the cancellation making the rejection moot with respect to claim 27.

III. The Invention as Claimed is Definite With Respect to the Requirements of 35 U.S.C. §112, second paragraph.

Claims 1-6, 9-14, 17-24 and 30-31 stand rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter Applicants regard as their invention. Applicants thank the Examiner for the suggestions offered with respect to overcoming the rejections. In general, Applicants assert the claims were definite and were patentable as such, however, to advance the prosecution, and to clarify the claims without narrowing, the following amendments were made.

Claims 1 and 2 were deemed indefinite for the recitation of "NPPB." Claim 1 has been amended to reflect the full name of the compound to provide a reference. Applicants respectfully submit that in view of the amendment to claim 1, one of skill in the art would understand the term NPPB, as it used in the art. Applicants respectfully assert that the claims as amended are definite and meet the requirements of 35 U.S.C. §112, second paragraph, thus Applicants respectfully request reconsideration and withdrawal of the rejection.

Claim 2 was rejected for recitation of the allegedly indefinite term "preferentially." While Applicants assert that those of skill in the art understand the term as used in the claim,

[illegible] Applicants respectfully request withdrawal of the rejection.

Claim 3 has been amended herein to include the recitation "wherein the nucleic acid

. ." to clarify the reference to the length in nucleotides. In view of the requested amendment, Applicants respectfully request withdrawal of the rejection as moot.

Claim 6 stands rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite for the recitation "cDNA." While the Applicants respectfully assert that the claim as written was definite as the nucleic acid could *both* be a cDNA, and comprise the coding region of SEQ ID NO:1 or SEQ ID NO:10, in order to advance prosecution, the claim has been amended to recite "DNA." Applicants respectfully request withdrawal of the rejection in view of the amendment.

Claim 9 was deemed indefinite for the recitation of an improper article and has been amended to recite "An expression cassette. . ." The claim was further deemed indefinite for the recitation of "a pIPAC gene coding sequence" which has been amended to recite "the coding sequence of a pIPAC gene." In view of the amendments, Applicants respectfully request withdrawal of the rejection.

Claims 11 and 12 were each deemed indefinite for the recitation "in which." Applicants have amended to Examiner's preferred recitation, "wherein," thus obviating the grounds of the rejection. Applicants respectfully request withdrawal of the rejection in view of the amendment.

Claims 17 19 were deemed indefinite for depending from a cancelled claim. Claim 17 has been rewritten so as to eliminate the dependency from claim 15, thus rendering the rejection moot for claim 17, as well as claims 18-19 dependent thereon. Applicants respectfully request withdrawal of the rejection.

[illegible] for recitation of a "reproductive unit" and a

been corrected. Applicants respectfully assert that the claim as amended is definite.

Applicants respectfully request reconsideration and withdrawal of the rejection.

Claims 18 and 19 were deemed indefinite, as the Office Action alleged that it was not clear as to whether the recited "reproductive unit" and "cell" contained the transgene. Applicants have amended claims 18 and 19 to reflect that the respectively recited "seed" and "cell" contain the expression cassette with the transgene of interest.

Claim 20 was deemed indefinite for the recitation of "molecule" without antecedent basis in claim 1. The claim has been amended to remove the recitation of "molecule," thus obviating the rejection. The Applicants respectfully request the rejection be withdrawn.

Claims 20 and 28 were deemed indefinite because the Office Action alleges that is unclear how a nucleic acid molecule is operably linked to a vector. The language "operably linked" has been amended to "inserted in." Applicants respectfully assert that the claims as amended are definite and respectfully request the rejection be withdrawn.

Claims 23 and 31 were allegedly indefinite for failure to recite the term "plant" after the "transformed." Although this limitation was inherent, as a plant cannot be regenerated from a cell which is not a plant cell, the claims have been amended to recite "transformed plant. . ." to clarify which cell was being regenerated into a plant. The Applicants respectfully assert that the rejection is moot in view of the amendment to the claim. Accordingly, withdrawal of the rejection is respectfully requested.

Claim 24 was allegedly unclear because "a "nucleic acid molecule of at least 20 nucleotides in length" cannot have a sequence of SEQ ID NO:1 or 10. Applicants respectfully note the both SEQ ID NO: 1 and 10 are, in fact, "nucleic acid molecules of at

acid, thus obviating the grounds of the rejection. Applicants have also inserted "nucleic acid"

before "sequence", to advance prosecution and for consistency purposes, noting that this term was inherent and would have been understood by one of skill in art reading the claim. Applicants thank the examiner for noting the typographical error of "regions," which was corrected to "region". Applicants respectfully request withdrawal of the rejection with respect to claim 24 and claims 28-31 dependent thereon, which Applicants respectfully assert are definite as written.

Claims 24 and 27 were deemed indefinite for failing to recite specific conditions for hybridization under conditions of moderate stringency. Applicants again note that claim 27 has been cancelled herein. The specification provides details of hybridization conditions, and the amendments are supported therein, for example on pages 22-24. In view of the amendments to include the requested conditions, the rejections with respect to that are moot.

Further with respect to claim 24, the Office Action also alleges that it is indefinite for recitation of "homologous" "identical" and "similar." Recitation of the term "homologous" has been amended to "identical" for consistency purposes. The Applicants respectfully assert that the terms "identical" and "similar" have clear meaning and are readily understood by those skilled in the art, and moreover, are clearly defined in the specification, for example at page 8, line 10 wherein it is stated:

> Nucleic acid sequences and amino acid sequences can be compared using computer programs that align the similar sequences of the nucleic or amino acids thus define the differences. For purposes of this invention, the DNAStar program (DNAStar, Inc., Madison, Wisconsin) and the default parameters used by that program are the parameters intended to be used herein to compare sequence identity and similarity. Alternately, the Blastn and Blastp 2.0 programs provided by the National Center for Biotechnology
>
> [illegible] may be used to determine the [illegible] identity and similarity between nucleic acid sequences and amino acid sequences.

Further, on page 9, at line 9 detailed definitions are provided:

> The terms "percent identical" and "percent similar" are also used herein in comparisons among amino acid and nucleic acid sequences. When referring to amino acid sequences, "percent identical" refers to the percent of the amino acids of the subject amino acid sequence that have been matched to identical amino acids in the compared amino acid sequence by a sequence analysis program. "Percent similar" refers to the percent of the amino acids of the subject amino acid sequence that have been matched to identical or conserved amino acids. Conserved amino acids are those which differ in structure but are similar in physical properties such that the exchange of one for another would not appreciably change the tertiary structure of the resulting protein. Conservative substitutions are defined in Taylor (1986, J. Theor. Biol. 119:205). When referring to nucleic acid molecules, "percent identical" refers to the percent of the nucleotides of the subject nucleic acid sequence that have been matched to identical nucleotides by a sequence analysis program.

Applicants respectfully submit that claim 24 is definite to one of skill in the art, in view of the amendments, and particularly when read in light of the specification. Thus the Applicants respectfully request reconsideration and the withdrawal of the rejection.

IV. The Claims, as Amended, Are Enabled, in Accordance With The Requirements of 35 U.S.C. §112, first paragraph.

Claims 1-4, 9-14, 17-24 and 27-31 stand rejected under 35 U.S.C. §112, first paragraph as not enabled by the teachings of the specification.

The Office Action acknowledges that the specification is enabling for the isolated nucleic acid molecule of SEQ ID NO:1 or 10 encoding SEQ ID NO:2, an expression cassette comprising said nucleic acid molecule operably linked to a promoter, a vector comprising

[illegible]

nucleic acid encoding any plant p-glycoprotein that is inducible by exposure of the plant to

NPPB or a nucleic acid molecule of at least 20 nucleotides in length and having a sequence of SEQ ID NO:1 or 10 or a sequence having at least 60% homology thereto, or a sequence that hybridizes to SEQ ID NO:1 or 10 or a part thereof under undefined moderate stringency conditions, or a sequence encoding an amino acid sequence that is at least about 40%, 70% or 80% identical to SEQ ID NO:2 or a part thereof. Applicants respectfully traverse the rejection as applied to the presently amended claims.

The claims as amended are directed to an isolated nucleic acid which has the restriction endonuclease cleavage sites shown in Figure 7 for one or more restriction endonucleases, and which encodes a plant p-glycoprotein that is inducible by exposure of the plant to 5-nitro-2-(3-phenylpropamino) benzoic acid (NPPB).

Claims are further directed to an isolated nucleic acid having a sequence selected from: SEQ ID NO: 1 or SEQ ID NO:10; a nucleic acid sequence that is at least about 60% identical to the coding of regions of SQ ID NOs:1 or 10; a nucleic acid sequence encoding a p-glycoprotein and having a sequence hybridizing with SEQ ID NOs 1 or 10 under defined conditions; a nucleic acid sequence encoding a polypeptide having SEQ ID NO:2; a nucleic acid sequence encoding an amino acid sequence that is at least about 70% identical to SEQ ID NO:2; a nucleic acid sequence encoding an amino acid sequence that is at least about 80% similar to SEQ ID NO:2; a nucleic acid sequence encoding a p-glycoprotein comprising an amino acid sequence that is at least about 40% similar to residues 1-76, 613-669 or 1144-1161 of SEQ ID NO:2; and a nucleic acid sequence encoding a p-glycoprotein and hybridizing, under defined conditions, to a sequence encoding an amino acid sequence

[illegible] of SEQ ID NO:2

determination. Amgen, Inc. v. Hoechst Marion Roussel, Inc. *et al.*, No. 01-1191, 01-1218,

2003 U.S. App. LEXIS 118 at *48 (Fed. Cir. 2003). Before any analysis of enablement can occur, it is necessary for the examiner to construe the claims. The examiner should always look for enabled, allowable subject matter and communicate to Applicants what that subject matter is at the earliest point possible in the prosecution of the application. (MPEP 2164.04)

The Federal Circuit has consistently held that "the specification must teach those of ordinary skill in the art how to make and use the full scope of **the invention** without undue experimentation. In re Wright, 999 F.2d 1557,1561(Fed. Cir. 1993). The fact that a quantity of experimentation, even complex experimentation, may be required is not dispositive of the analysis (MPEP 2164.04). The key word is "undue," not "experimentation". Angstadt, 537 F.2d at 504. The factors to be considered in determining whether experimentation is undue include the breadth of the claims; the nature of the invention; the state of the prior art; the level of one of ordinary skill; the level of predictability in the art; the amount of direction provided by the inventor; the existence of working examples; and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988). It is improper to conclude that a disclosure is not enabling based on analysis of only one of the factors while ignoring one or more of the others. MPEP 2164.01(a).

Nevertheless, not everything necessary to practice the invention need be disclosed. The Federal Circuit has stated that what is well-known is best omitted. In re Buchner, 929 F.2d 660, 661 (Fed. Cir. 1991). Further, the scope of enablement must only bear a reasonable connection to the scope of the claims. See, e.g., In re Fisher, 427 F.2d 833, 839 (CCPA

2003 U.S. App. LEXIS 118 at *50.

In the instant case, the Office Action has set out subject matter deemed enabling and allowable, and Applicants wish to express their thanks to the Examiner. In view of the amendments, Applicants respectfully assert the claims are fully enabled.

Applicants respectfully note that it is well known to those of skill in the art that the genetic code is degenerate, and as such it is quite possible to have as little as 66% homology and have 100% identity in the encoded protein. It is very common for closely related organisms to have large divergences in sequences at the nucleic acid level -- this is even more known to be true on the plant kingdom. Thus, it is impossible to conclude that one of skill in the art could not make and use the nucleic acid of claims 1 and 24 for example because of the variation provided therein. The variation is well within art-expected and art-accepted norms.

For claim 1 in particular, as amended, the skilled artisan has substantial guidance in identifying the nucleic acid as a claimed structure through it restriction endonuclease maps. Restriction endonuclease mapping is a an art-excepted means of identifying a nucleic acid structure. Additionally, substantial functional information is provided which eliminates the concerns the Office Action expresses. The Applicants also respectfully point out that claim 1 should not be construed to require a functional p-glycoprotein, only one that meets the claim limitations of the proper restriction endonuclease sites and the inducibility upon exposure to NPPB. Thus claim 1 requires a functional nucleic acid but is in no way limited to a biologically functional p-glycoprotein.

The Office Action suggests that in view of the Wands factors, it would be unpredictable as to whether an isolated nucleic acid of the invention will encode a

or from SEQ ID NO: 2, respectively. The Office Action cites Lazar *et al.* (Mol. Cell. Biol.

3:1247-1252, 1988) and Broun *et al.* (Science 282:131-133, 1998). The Office Action alleges that the cited references teach unpredictability in DNA/protein function when one or more amino acids / bases in that protein is modified. Specifically, the Office Action cites the title of the Lazar reference as teaching that a mutation of aspartic acid 47 and leucine 48 of a transforming growth factor alpha results in different biological activities. While the Lazar reference may be indicative of the effects of mutating residues 47 and 48 may provide information on the relative importance of these particular residues in transforming growth factor, the instant claims contain no limitations to such changes, nor do Lazar *et al.* provide any evidence that the particular findings are to be generalized or interpreted as the state of the art in p-glycoproteins, or in fact, any plant protein whatsoever. Furthermore, Lazar *et al.* do teach that there is *only 35% homology* among the EGF-like peptides (rat, mouse and human EGF's and, rat and human TGFα's) and yet all share the same cellular receptor – which strongly suggests that a wide range of variation is normally acceptable and tolerated in biological systems.

The Office Action cites the abstract of the Broun reference as teaching that as few as four amino acid substitutions can change oleate 12-desaturase activity. Broun *et al.* teach that "comparison of the amino acid acid sequences of the hydroxylases from *L. fendleri* and *R. communis* with the sequences for oleate desaturases from *Arabidopsis, Zea mays, Glycine max* (two sequences), *R. communis* and *Brassica napus* revealed that only seven residues were strictly conserved in all of the six desaturases but divergent in both of the hydroxylases." This statement shows that even in closely related plants, as in known in the

exception, not the norm, in biological systems. This is further supported on general

principles, and the basic theory of evolution. While Broun *et al.* may be reflective of the state of the art in plant lipid synthesis enzymes, Applicants respectfully note that the focus of the Broun reference as a whole is on the catalytic plasticity of enzymes in biological systems, and plants in particular. Thus, Broun *et al.* do not address the predictability of varying the nucleic acid sequences of the present invention, nor the proteins encoded therein and generalizations from Broun (if any) would support the idea that most modifications would be benign. Further to this idea, Applicants also cite Service (Science 277: 179, 1997) for the proposition that a protein's amino acid sequence may be altered by up to 70%, yet virtually always folds up into the same 3D structure. A copy is provided herewith.

Applicants respectfully assert that the publications cited in the Ofice Action do not advance the Office Action's assertion that the current claims are not adequately enabled so as to teach those of skill how to make and use isolated nucleic acids of, for example, claims 1 and 24. The cited references do not address predictability in modifying p-glycoproteins; they do not address predictability in modifying nucleic aicds encoding such proteins; nor do they touch on inducibility by NPPB exposure. They do not identify what information is allegedly missing from the instant specification, or why one skilled in the art could not supply the information without undue experimentation and they provide no specific technical reasons for the rejection. The cited art does not advance the position taken as to unpredictability in the relevant art, and here, simply cannot support a *prima facie* case of lack of enablement.

The Applicants respectfully submit that the Office Action's reliance on Amgen v. Chugai is misplaced. In that case, conception was regarded to occur simultaneously with

stated ". . .we do not intend to imply that generic claims to genetic sequences cannot be valid

where they are of a scope appropriate to the invention disclosed by an applicant. That is not the case here, where Amgen has claimed every possible analog of a gene containing about 4,000 nucleotides, with a disclosure only of how to make EPO and a very few analogs." In the claim in question, there were solely functional limitations, and no structural limitations whatsoever. The case here is different, the structural limitations with respect to the required restriction endonuclease cleavage sites, in combination with the functional description, greatly limits the possible sequences covered by the claim and enables one of skill to make and use the claimed nucleic acids commensurate with the disclosure.

In sum, with respect to the rejection for the lack of enablement, it is respectfully submitted that the Office Action does not establish any grounds to support the contention that undue experimentation would be required, or that insufficient guidance is provided to enable those of skill in the art to make and use the invention as claimed. The Applicants assert that the claims, as amended, are fully enabled in accordance with 35 U.S.C. §112 and that no undue experimentation is required for a skilled artisan to practice claims 1, 24 or any of the claims. Accordingly, Applicants respectfully request withdrawal of the rejection for lack of enablement under 35 U.S.C. §112, first paragraph.

V. The Claims, as Amended, Satisfy The Written Description Requirement of 35 U.S.C. §112, first paragraph.

Claims 1-4, 9-14, 17-24 and 27-31 stand rejected under 35 U.S.C. §112, first paragraph as allegedly not described in such a way as to reasonably convey to one of skill in

the Office Action alleges that claims are broadly drawn to any plant polypeptide

gene including those from Arabidopsis thaliana and Brassica napus, a multitude of sequences

with 60% homology, 70% identity, 405 or 80% similarity to SEQ ID NOs 1, 2 or 10 or fragments thereof, as well as hybridizing sequences thereof having no known activity.

The Office Action alleges that the instant specification only provides guidance for the isolated nucleotide sequence of SEQ ID NOs:1 or 10 encoding SEQ ID NO:2. Further alleged is that no description of specific chemical or physical characteristics for all plant p-glycoprotein genes or proteins which would allow one of skill in the art to predictably determine what the structure of the nondisclosed sequences would be. Applicants respectfully traverse this rejection with respect to the claims as amended.

The adequacy of a written description is a question of fact which must be determined on a case-by case basis. MPEP 2163. A written description is given a strong presumption of adequacy and rejection of original claims for lack of written description should be rare. Id. An examiner must overcome the presumption of adequacy by putting forth, on a reasonable basis, sufficient evidence or reasoning. In re Wertheim, 541 F.2d 257, 263 (CCPA 1976). Arguing lack of literal support is not enough since the invention need not be described in *ipsis verbis* to satisfy the written description requirement. Id. at 265.

As the Federal Circuit has stated: ". . .the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." Vas-Cath Inc. *et al.* v. Mahurkar *et al.*, 935 F.2d 1555, 1563-4 (Fed. Cir. 1991) (emphasis in original). See also Regents of the Univ. of Cal. v. Eli Lilly & Co., 119

perspective from which satisfaction of the requirement is measured. Amgen Inc. v. Hoechst

Marion Roussel, Inc. *et al.*, No. 01-1191, 01-1218, 2003 U.S. App. LEXIS 118 at *35 (Fed. Cir. 2003) citing Lockwood v. Am. Airlines, Inc., 107 F.3d 1565, 1572 (Fed. Cir. 1997); see also MPEP 2163. The written description inquiry, therefore, focuses on a comparison between the specification and the invention referenced by the terms of the claim. Id. at *39.

Possession of the invention may be established through words, structures, figures, diagrams and formulas which fully set forth the claimed invention. Lockwood, 107 F.3d at 1572. "Generally there is an inverse correlation between the level of skill and knowledge in the art and the specificity of the disclosure necessary to satisfy the written description requirement." MPEP 2163.

Here the Applicants have disclosed two gene sequences, a cDNA sequence, and the sequence of the encoded amino sequence, detailed restriction endonuclease cleavage maps for at least 40 restriction enzymes, and comparative analysis of related sequences from six other organisms, as well as a consensus sequence. The claimed invention relates to an isolated nucleic acid having a restriction endonuclease cleavage sites for one or more of the restriction enzymes provided in Figure 7, and which encodes a plant p-glycoprotein inducible when the plant is exposed to NPPB. Accordingly, the skilled artisan can envision the claimed structures in accordance with the specification and would understand that the inventors were in possession of the claimed invention at the time of filing.

The Federal Circuit has steadfastly refused to require sequences in all cases of claims to genetic material. "[M]ore recently in Enzo Biochem, we clarified that Eli Lilly did not [illegible] of genetic material fail as a matter of law to meet the

of the art the disclosed function is sufficiently correlated to a particular, known structure."

Amgen, 2003 U.S. App. LEXIS 118 at *41.

Here, in accordance with the holding in Amgen, sufficient information has been conveyed such that those of skill in the art would recognize the description of the molecules. The specification conveys, to those of skill in the art, distinguishing information concerning the identity of the molecules such that one of skill could visualize or recognize the identity of the members of the genus of claimed nucleic acids. For example, the specification discloses the functional information, as well the structural information required for the skilled artisan to correlate the function with known structures – i.e. NPPB-inducible p-glycoprotein-encoding genes with restriction maps which match those the specification provides. Nothing more is required.

The Office Action must properly weigh all factors including partial structure, physical/chemical properties, functional characteristics, known or disclosed correlations between structure and functions, methods of making, and combinations of the above in view of the level of skill and knowledge in the art in determining whether one of skill would recognize that applicant was in possession of the invention. The specification describes the nucleic acids sufficiently so as to satisfy the written description requirements 35 U.S.C. §112, as well as the policies behind it. The specification clearly conveys that the Applicants have invented the claimed subject matter; the public is put in possession of what was invented; and there is a *quid pro quo* for the patent rights sought. In view of the foregoing, the Applicants respectfully request the withdrawal of the rejection for lack of adequate written description under 35 U.S.C. §112.

remarks, the presently pending claims are believed to be in condition for allowance.

Applicants respectfully request early and favorable reconsideration and withdrawal of the objections and rejections set forth in the October 2, 2002 Official Action, and allowance of this application.

Respectfully submitted,

Date: March 3, 2003

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

Please replace the paragraph beginning on page 8, line 2 with the following rewritten paragraph:

With respect to RNA molecules of the invention the term "isolated nucleic acid" primarily refers to an RNA molecule encoded by an isolated DNA molecule as defined above. Alternatively, the term may refer to an RNA molecule that has been sufficiently separated from RNA molecules with which it would be associated in its natural state (i.e., in cells or tissues), such that it exists in a "substantially pure" form (the term "substantially pure" is defined below). Nucleic acid sequences and amino acid sequences can be compared using computer programs that align the similar sequences of the nucleic or amino acids thus define the differences. For purposes of this invention, the DNAStar program (DNAStar, Inc., Madison, Wisconsin) and the default parameters used by that program are the parameters intended to be used herein to compare sequence identity and similarity. Alternately, the Blastn and Blastp 2.0 programs provided by the National Center for Biotechnology Information ([at http://www.ncbi.nlm.nih.gov/blast/ ;] Altschul et al., 1990, J Mol Biol 215:403-410) using a gapped alignment with default parameters, may be used to determine the level of identity and similarity between nucleic acid sequences and amino acid sequences.

[illegible] Brief Description of the Drawings

page 6, line 29 with the following rewritten paragraphs:

[**Figure 1.**] **Figures 1 - 4.** Amino acid sequence lineup of ATPAC deduced amino acid sequence and the amino acid sequences of related mammalian and plant genes. The lineup shows the ATPAC deduced amino acid sequence (SEQ ID NO:2) compared with (1) hmdr1 (SEQ ID NO:3); (2) mmdr1 (SEQ ID NO: 4); (3) hmdr3 (SEQ ID NO:5); (4) mmdr2 (SEQ ID NO:6); (5) atpgp1 (SEQ ID NO:7); and (6) atpgp2 (SEQ ID NO:8). A consensus sequence (SEQ ID NO: 9) is also shown. **Figure 1.** Amino acids corresponding to 1-440 of the consensus sequence. **Figure 2.** Amino acids corresponding to 441-880 of the consensus sequence. **Figure 3.** Amino acids corresponding to 881-1210 of the consensus sequence. **Figure 4.** Amino acids corresponding to 1211-1325 of the consensus sequence.

[**Figure 2.**] **Figure 5.** Graph depicting the effect of rhodamine 6G on the growth rate of cells transformed with and expressing ATPAC as compared with control cells not containing ATPAC.

[**Figure 3.**] **Figure 6.** Restriction map of genomic clone of ATPAC, SEQ ID NO:10.

[**Figure 4.**] **Figure 7.** Restriction map of cDNA clone of ATPAC, SEQ ID NO:1.

Please replace the paragraph beginning at page 13, line 11 with the following rewritten paragraph:

A genomic clone of ATPAC (SEQ ID NO:10) has also been isolated from a bacterial artificial chromosome (BAC) library of the Arabidopsis genome (BAC clone IGF F3J22,

plasmid vector (pBluescript). A restriction map of ATPAC is found in Fig. [3] 6. The

corresponding cDNA clone of ATPAC is found in SEQ ID NO:1 and its restriction map is Fig. [4] 7.

Please replace the two paragraphs beginning at page 14, line 27 with the following rewritten paragraphs:

In other preferred embodiments, the nucleic acids have a restriction digest map that is identical for at least 3 enzymes (more preferably 6 enzymes and most preferably 9 enzymes) to the maps shown in Figs. [3 or 4] 6 or 7. In another preferred embodiment, the nucleic acids have a restriction digest map identical to those shown in Fig. [3] 6 for enzymes XhoI, XcmI and SpeI (preferably additionally SacI, PacI and BsaI, and most preferably additionally AclI, BanI and SnaBI).

In another preferred embodiment, the nucleic acids have a restriction digest map identical to those shown in Fig. [4] 7 for enzymes XbaI, TatI and NciI (preferably additionally DraI, BsmI and BclI, and most preferably additionally AccI, BsgI and TliI). The nucleic acids of the invention are at least 20 nucleic acids in length (preferably at least 50 nucleic acids and most preferably at least 100 nucleic acids).

Please replace the paragraph beginning at page 22, line 13 with the following rewritten paragraphs:

[illegible] may be identified by using hybridization and washing conditions of appropriate stringency.

For example, hybridizations may be performed, according to the method of Sambrook et al., using a hybridization solution comprising: 5X SSC, 5X Denhardt's reagent, 1.0% SDS, 100 [¼g/ml] μg/ml denatured, fragmented salmon sperm DNA, 0.05% sodium pyrophosphate and up to 50% formamide. Hybridization is carried out at 37-42 C for at least six hours. Following hybridization, filters are washed as follows: (1) 5 minutes at room temperature in 2X SSC and 1% SDS; (2) 15 minutes at room temperature in 2X SSC and 0.1% SDS; (3) 30 minutes-1 hour at 37 C in 2X SSC and 0.1% SDS; (4) 2 hours at 45-55 C in 2X SSC and 0.1% SDS, changing the solution every 30 minutes.

One common formula for calculating the stringency conditions required to achieve hybridization between nucleic acid molecules of a specified sequence homology (Sambrook et al., 1989):

Please replace the paragraph beginning at page 23, line 13 with the following rewritten paragraph:

The stringency of the hybridization and wash depend primarily on the salt concentration and temperature of the solutions. In general, to maximize the rate of annealing of the probe with its target, the hybridization is usually carried out at salt and temperature conditions that are 20-25 C below the calculated Tm of the of the hybrid. Wash conditions should be as stringent as possible for the degree of identity of the probe for the target. In general, wash conditions are selected to be approximately 12-20 C below the Tm of the

100 [¼g/ml] μg/ml denatured salmon sperm DNA at 42 C, and wash in 2X SSC and 0.5%

SDS at 55 C for 15 minutes. A high stringency hybridization is defined as hybridization in 6X SSC, 5X Denhardt's solution, 0.5% SDS and 100 [¼g/ml] μg/ml denatured salmon sperm DNA at 42 C, and wash in 1X SSC and 0.5% SDS at 65 C for 15 minutes. A very high stringency hybridization is defined as hybridization in 6X SSC, 5X Denhardt's solution, 0.5% SDS and 100 [¼g/ml] μg/ml denatured salmon sperm DNA at 42 C, and wash in 0.1X SSC and 0.5% SDS at 65 C for 15 minutes.

Please replace the paragraph beginning at page 34, line 1 with the following rewritten paragraph:

The plPAC of the present invention was identified by its up-regulation in response to a chloride ion channel blocker. *Brassica napus* plants were grown either in the presence or absence of 20 [¼M] μM 5-nitro-2-(3-phenylpropylamino) benzoic acid (NPPB). After five days, the roots of the seedlings were harvested and total RNA was extracted separately from the treated and untreated plants. From the total RNA preparations, poly (A)+ RNA was isolated and used as the starting material to create a cDNA subtraction library, using the CLONTECH PCR-SELECTJ cDNA Subtraction Kit and accompanying instructions (CLONTECH Laboratories, Inc., Palo Alto, CA).

Please replace the paragraph beginning at page 34, line 22 with the following rewritten paragraph:

deduced amino acid sequence encoded by SEQ ID NO:1 is shown in [Figure 1] Figures 1-4

as "atpac" (SEQ ID NO:2), in a lineup with the following sequences: (1) hmdr1 (SEQ ID NO:3); (2) mmdr1 (SEQ ID NO:4); (3) hmdr3 (SEQ ID NO:5); (4) mmdr2 (SEQ ID NO:6); (5) atpgp1 (SEQ ID NO:7); and (6) atpgp2 (SEQ ID NO:8). A consensus sequence (SEQ ID NO:9) is also shown.

Please replace the paragraph beginning at page 35, line 21 with the following rewritten paragraph:

The compound Rhodamine 6G is a well known substrate of mammalian p-glycoproteins (Kolaczkowski et al., J. Biol. Chem. 271: 31543-31548, 1996). The ability of a cell to detoxify the compound is indicative of activity of p-glycoproteins. A bacterial cell line was transformed with an expression vector comprising ATPAC. The growth rate of transformed and non-transformed cells was then measured, in the presence or absence of Rhodamine 6G. Results are shown in Figure [2] 5. As can be seen, ATPAC-expressing cells grown in the absence of the drug had the best growth rate. Moreover, even in the presence of the drug, the cells grew more quickly than non-transformed cells in the presence or absence of Rhodamine 6G. These results demonstrate that ATPAC encodes a functional and robust p-glycoprotein.

In the claims:

1. (Amended) [A] An isolated nucleic acid [isolated from a plant], which has the restriction endonuclease cleavage sites shown in Figure 7 for one or more restriction endonucleases, and which encodes a plant p-glycoprotein that is inducible by exposure of [the] a plant to [NPPB] 5-nitro-2-(3-phenylpropylamino) benzoic acid (NPPB).

2. (Amended) The isolated nucleic acid of claim 1, which is [preferentially] expressed in plant roots upon exposure of the plant to NPPB.

3. (Amended) The isolated nucleic acid of claim 1, wherein the plant is [selected from the group consisting of] *Brassica napus* [and] or *Arabidopsis thaliana* and wherein the nucleic acid is 3850-4150 nucleotides long.

4. (Amended) The isolated nucleic acid of claim 1, which has the restriction endonuclease cleavage sites shown in Figure [4] 7 for at least three [enzymes] restriction endonucleases.

6. (Amended) The isolated nucleic acid of claim [5] 1, [which] wherein the nucleic acid is a [cDNA] DNA comprising a coding region [selected from the group consisting] of SEQ ID NO:1 [and] or SEQ ID NO:10.

9. (Amended) [A] An expression cassette, which comprises a [plPAC gene] coding

11. (Amended) The expression cassette of claim 10, [in which] wherein the promoter

is the cauliflower mosaic virus 35S promoter.

12. (Amended) The expression cassette of claim 10, [in which] wherein the pIPAC gene is part or all of SEQ ID NO:1 or SEQ ID NO:10.

17. (Amended) A transgenic plant comprising the expression cassette of claim 9 [produced by the method of claim 15] wherein the plant has enhanced resistance to xenobiotic compounds.

18. (Amended) A [reproductive unit form] seed from the transgenic plant of claim 17, said seed comprising the expression cassette..

19. (Amended) A cell from the transgenic plant of claim 17, said cell comprising the expression cassette.

20. (Amended) A recombinant DNA molecule comprising the nucleic acid [molecule] of claim 1, [operably linked to] inserted in a vector for transforming cells.

23. (Amended) A transgenic plant regenerated from the transformed plant cell of claim 22.

[illegible]

a) SEQ ID NO:1 [and] or SEQ ID NO:10;

b) a nucleic acid sequence that is at least about 60% [homologous] identical to the coding regions of SEQ ID NO:1 or SEQ ID NO:10;

c) a nucleic acid sequence encoding a p-glycoprotein and hybridizing with SEQ ID NO:1 or SEQ ID NO:10 [at moderate stringency] under conditions comprising hybridization in 6X SSC, 5X Denhardt's solution, 0.5% SDS and 100 µg/ml denatured salmon sperm DNA at 42 C and washing in 2X SSC and 0.5% SDS at 55 C for 15 minutes;

d) a nucleic acid sequence encoding [part or all of] a polypeptide having SEQ ID NO:2;

e) a nucleic acid sequence encoding an amino acid sequence that is at least about 70% identical to SEQ ID NO:2;

f) a nucleic acid sequence encoding an amino acid sequence that is at least about 80% similar to SEQ ID NO:2;

g) a nucleic acid sequence encoding a p-glycoprotein comprising an amino acid sequence that is at least about 40% similar to residues 1-76, 613-669 or 1144-1161 of SEQ ID NO:2; and

h) a nucleic acid sequence encoding a p-glycoprotein and hybridizing [at moderate stringency] to a sequence encoding residues 1-76, 613-669 or 1144-1161 of SEQ ID NO:2 under conditions comprising hybridization in 6X SSC, 5X Denhardt's solution, 0.5% SDS and 100 µg/ml denatured salmon sperm DNA at 42 C and washing in 2X SSC and 0.5% SDS at 55 C for 15 minutes.

28. (Amended) A recombinant DNA molecule comprising the nucleic acid

31. (Amended) A transgenic plant regenerated from the plant cell of claim 30.